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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,404	MCMILLAN ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 50-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 50-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been docketed to Primary Examiner Bradley L. Sisson.

Specification

2. The specification is objected to as documents have been improperly incorporated by reference. In particular, the specification states at page 66 that International Publication Number 99/48608 "is incorporated by reference herein." Such omnibus language fails to specify what specific information applicant seeks to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited documents. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly

> incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Accordingly, the cited documents are not considered to have been properly incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5 and 50-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012

[10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

5. For convenience, claims 1 and 50, the only independent claims, are reproduced below.

Claim 1 (currently amended): An apparatus for determining a threshold cycle number in a nucleic acid amplification reaction, the apparatus comprising:

a) at least one detection mechanism for measuring, at a plurality of different times during the amplification reaction, at least one signal whose intensity is related to the quantity of a nucleic acid sequence being amplified in the reaction; and

b) a controller in communication with the detection mechanism, wherein the controller is programmed to perform the steps of:

i) deriving a growth curve from the measurements of the signal;

ii) calculating a derivative of the growth curve;

iii) identifying a characteristic of the derivative; and

iv) determining [a] the threshold cycle number associated with the characteristic of the derivative.

Claim 50 (currently amended): An apparatus for determining a threshold cycle number in a nucleic acid amplification reaction, the apparatus comprising:

a) at least one detection mechanism for measuring, at a plurality of different times during the amplification reaction, at least one signal whose intensity is related to the quantity of a nucleic acid sequence being amplified in the reaction; and

b) a controller in communication with the detection mechanism, wherein the controller is programmed to perform the steps of:

i) storing signal values defining a growth curve for the nucleic acid sequence, wherein the growth curve expresses signal intensity as a function of cycle number in the reaction;

ii) determining a derivative of the growth curve, wherein the derivative is determined with respect to cycle number; and

iii) calculating [a] the threshold cycle number associated with a characteristic of the derivative.

6. For purposes of examination, the claims have been interpreted as encompassing a device comprising al elements so to permit the determination of a threshold number of cycles of nucleic

acid amplification to be conducted where said nucleic acid amplification encompasses, but is not limited to:

- Asymmetric amplification,
- Multiplex amplification,
- Nested-multiplex amplification, and
- Amplification where the polymerase used has low fidelity and the intended/desired product is but a subtraction of the total population of amplicons

7. As presently worded. The "apparatus" comprises but two elements, a detection mechanism, e.g., a CCD, and a controller that has been programmed. A review of the disclosure fails to find an adequate written description of an apparatus for determining a threshold cycle number of amplification where the device comprises but these two elements. Indeed, as presently worded, the controller is not in communication with any element and as such, it is not possible for it to exert any control over any aspect of the apparatus. The apparatus also does not comprise any means by which said threshold cycle number is able to be determined for there is nothing that the detection mechanism is to detect. Even if there was something for the detection mechanism to detect, the controller does not report out or display such a value. Consequently, the two elements by themselves are not considered to constitute the basic elements of the claimed apparatus.

8. As presently worded, the claimed apparatus could comprise a reaction vessel of virtually any size. A review of the specification fails to find adequate support for such breadth of scope. In support of this position, attention is directed to page 28, last paragraph, which states that the reaction vessel can have a chamber with a length of from 1 to 15 mm, and a width of from 1.4 to

20 mm, and a thickness in the range of 0.5 to 5 mm. The specification does not reasonably support a device that comprises an infinite number of elements and where the reaction chamber of the apparatus can be of virtually dimension.

9. For the above reasons, the specification does not reasonably suggest that applicant was in possession of the clamed invention at the time of filing. Therefore, and in the absence of convincing evidence to the contrary, claims 1-5 and 50-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

10. Claims 1-5 and 50-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737,

> 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

As noted above, the specification does not provide an adequate written description of the apparatus so as to reasonably suggest that applicant was in possession of same at the time of filing. Further, and as presented above, the apparatus as defined by the claims, lacks certain essential elements so as to render it functional. The specification has not been found to set forth a reproducible procedure whereby the claimed apparatus would be able to accurately determine any threshold number of cycles of nucleic acid amplification are to be performed when there is but one amplicon to be produced. The specification is essentially silent as to how the skilled artisan is to program and utilize the device when conducting asymmetric amplification, nested PCR, and/or nested asymmetric PCR. The specification is also silent as to how the claimed apparatus is to be used when the polymerase being utilized introduces errors in terms of nucleotide incorporation and/or premature termination, thereby resulting in limited number of accurate copies of amplicons in a population of significantly greater numbers of incomplete or erroneous amplicons. In support of this position, attention is directed to US Patent Application Publication 2003/0228596 A1 (Liu et al.), which teaches at paragraph 4:

> Allele-dropout and polymerase error are significant problems in single cell amplifications. In addition, the sensitivity of allele-specific PCR for detecting rare mutations is limited by the exponential amplification of any mismatch extensions.

The specification of the instant application is essentially silent as to how the claimed apparatus is to take these art-recognized difficulties into consideration and accurately and reproducibly

determine the correct threshold number of cycles of amplification that are to be performed for any sample or combination of samples.

11. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, claims 1-5 and 50-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-5 and 50-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claims 1-5 and 50-94 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: those elements that permit the artisan to control the various aspects of the cycles of amplification, e.g., temperature, duration, temperature ramp time, volume of reagents, frequency of measurement, communication means between the controller and the elements to be controlled.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-5 and 50-94 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 6,713,297 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an apparatus comprising at least one detection mechanism and at least one controller where the controller has been programmed to measure the amount of nucleic acid template present in a sample and to determine the threshold cycle number.

Claim Rejections - 35 USC § 101

17. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

18. Claims 1-5 and 50-94 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. As presently worded, the claimed apparatus is to determine a threshold cycle number in a nucleic acid amplification reaction. The claimed apparatus, however, is void of any reaction chamber, or communicating means, or any other means that would allow for any measurement, much less the control of the detection mechanism.

In view of the loose assortment of elements, and the utter absence of any chamber in which a measurement is to be taken. It is not possible for the claimed apparatus to function in the manner set forth in the preamble of the claims. Therefore, and in the absence of convincing evidence to the contrary, claims 1-5 and 50-94 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility.

Conclusion

19. Rejections and/or objections that appeared in the prior Office action and which were not repeated hereinabove have been withdrawn.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
26 June 2004